Epitomes

Important Advances in Clinical Medicine

Psychiatry

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The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in psychiatry. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, as to both scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of these items of progress in psychiatry that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Psychiatry of the California Medical Association, and the summaries were prepared under the direction of Dr Rosenfeld and the Panel.

Advances in Mood Stabilizing Medications

IN THE PAST DECADE, lithium's limitations as an acute and prophylactic treatment for patients with manic-depressive illness have been recognized. In addition, studies have revealed that about 50% of patients may show only a partial therapeutic response and inadequate prophylactic effect. Certain diagnostic subtypes (dysphoric mania, rapid cycling) have notably poor response rates to lithium therapy,and a substantial number of patients cannot tolerate its side effects or are unable to achieve blood levels that are necessary for complete suppression of symptomatology. This experience has necessitated the study of adjunctive and alternative treatment options to lithium.

Several anticonvulsants have emerged as major mood stabilizing alternatives to lithium therapy for bipolar illness. Data on carbamazepine and valproate indicate that while they appear to prevent manic and depressive episodes in patients inadequately responsive to lithium carbonate, they may not be sufficient for monotherapy. Two newer anticonvulsant agents, gabapentin and lamotrigine, have shown promise in the treatment of patients with bipolar disorders. Both gabapentin and lamotrigine differ from other mood regulators in two major ways: (1) their reported frequent effectiveness for treating resistant patients, and (2) their relatively benign side-effect profiles that make discontinuation due to side effects rare.

Gabapentin increases gamma amino butyric acid (GABA) turnover and whole blood serotonin, increases breakdown of glutamic acid, and modulates norepinephrine and dopamine in vivo. Case reports have described its potential psychiatric indications in bipolar disorder, panic disorder, generalized anxiety disorder and behavioral dyscontrol. The post-absorption half-life is 5–7 hours with rapid crossing of the blood brain barrier. The usual starting dose of gabapentin is 300 mg once a day; the dose is increased and rapidly titrated every three to five days to the mood stabilizing dose, which is most often between 900–2700 (up to 4800 reported) mg per day typically taken in divided doses. Therapeutic effect is noticed from within a week up to a month. Gabapentin is generally well tolerated. The most common side effects are sedation, dizziness, unsteadiness, nystagmus, ataxia, fatigue, tremor and diplopia, which stop when the drug is stopped.

Lamotrigine acts upon the voltage-dependent sodium channels, resulting in inhibited release of the excitatory neurotransmitters glutamate and aspartate, and stabilization of the neuronal membranes. Early reports suggest that lamotrigine may be beneficial in patients with treatment-resistant bipolar disorders, including mixed and rapid cycling illness. Its use in treating unipolar depression and anxiety disorders has not been extensively studied. The inhibition of glutamate may suggest a role for lamotrigine in mania following ischemic stroke. Usual initiating dose of lamotrigine is 25 mg once or twice a day, and this is increased by 25–50 mg every 1–2 weeks, to reach the usual effective dose range of 100–200 mg per day. Therapeutic effect is generally noticed within a month of starting treatment. The most commonly reported adverse effects of lamotrigine are dizziness, diplopia, ataxia, blurred vision, nausea, and vomiting. A severe morbilliform or maculopapular rash, developing within the first six weeks which is related to starting dose and escalation of titration, can be a special clinical hazard (rate in adults one in every thousand patients with higher incidence below age sixteen). These effects subside when medication is discontinued, but can be problematic to treat.

The principal advantage of gabapentin and lamotrigine over lithium is that routine serum monitoring of drug levels is not essential during therapy. However, as with all bipolar patients, one should be aware of a possible paradoxical switch to mania or provocation of rapid

cycling. Also, while gabapentin may be safely used in combination with depakote and carbamazepine, their doses need adjustment when lamotrigine is initiated. Valproic acid should be reduced in dosage before starting lamotrigine to decrease inhibition of metabolism and reduce the risk of rash. Due to enzyme induction, the dose of carbamzepine may need to be reduced when lamotrigine treatment is initiated. The relatively recent use of gabapentin and lamotrigine for mood disorders limits the information regarding their long term therapeutic efficacy, and potential emergent side effects.

Other modalities being studied as mood stabilizers include calcium channel blockers, and thyrotropin releasing hormone (TRH) plus other endogenous neuropeptides. Calcium channel blockers like verapamil and nimodipine are showing special promise for rapid and ultra rapid cycling. Preliminary findings have suggested that the dihydropyridine class of L-type calcium channel blockers, which includes nimodipine, isradipine etc., compared to the phenylalkalamine verapamil may have greater mood stabilizing effects, and potential as an alternative or adjunct to lithium. Preliminary data on TRH indicate possible acute anti-depressant, anti-anxiety, and anti-suicide effects.

Although the search for safer alternatives to lithium therapy in affective disorders is increasingly promising, further research of the newer mood stabilizing medications is warranted in order to establish their safety and efficacy.

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Traumatic Disorders—Contemporary Directions

EMOTIONAL REACTIONS to trauma have been recorded since ancient times. In this century, the study of World War I veterans ("shell shock"), World War II consequences ("traumatic neurosis"), and later DSM-I (Gross Stress Reaction), DSM-II ("Transient Situational Disturbance"), Holocaust Survivors ("Survivors' Syndrome"), and DSM-III (PTSD) all constituted additions to a crystallized modern understanding of trauma reactions.

Since 1980, when Post Traumatic Stress Disorder (PTSD) became part of the official psychiatric nomenclature (DSM-III), a concerted effort has been made by specialists in psychiatric trauma to legitimize PTSD as a complex psychiatric disorder. Trauma can result in a range of disorders. The most commonly associated conditions with trauma are: PTSD, Acute Stress Disorder, other Anxiety Disorders, Mood Disorders, Somatization Disorders, Dissociative Disorders, Substance Abuse, and Adjustment Disorders. On the other hand, early childhood exposure to severe trauma more often results in affective psychopathology with little resemblance to PTSD. The type of traumatic psychopathology may be determined by the interaction of factors: type of trauma, age of impact, preexisting biological vulnerability, and possibly the complexity of affected brain mechanisms.

Diagnosis of Post Traumatic Stress Disorder represents the prototype of traumatic disorders. The symptomatology includes a classical triad of symptoms: a) The re-experiencing of the traumatic event, b) Both persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness, c) Symptoms of hyperarousal (difficulty falling asleep, insomnia, irritability, angry outbursts, etc.). These symptoms occur after the exposure via experiencing, witnessing, or confronting an event that is perceived as threatening and is accompanied by intense fear, horror, and helplessness. Prevalence of PTSD is 7.2 percent in the generation population. Between 50 and 90 percent of patients with PTSD have comorbid disorders such as anxiety, depression and alcohol abuse.

Other traumatic disorders include acute stress disorder, a condition that resembles PTSD but is characterized by a one-month duration (following the trauma) and includes significant dissociative symptoms. Anxiety disorders (more often panic disorders and generalized anxiety) are often the main psychiatric manifestation after traumatic stress. Most anxiety disorders occur more often in combination with other diagnoses rather than "pure culture" clinical forms. While, for example, major depression may not exhibit a different picture after a known traumatic stress, a history of traumatic stress may add additional biological abnormalities and may thus influence significantly the outcome of treatment.

After major traumatic events such as a catastrophe affecting an entire community, PTSD is relatively rare. Emotional manifestations of some kind are common, however. The majority of traumatized individuals will present a transient benign reaction characterized by terror, a sense of unreality, some depersonalization, some re-experiencing, transient anxiety, a sense of loss, and some preoccupation with images of the trauma that subsides within about 3 to 4 months. Risk factors for patients to PTSD after a community trauma include past psychiatric history, family psychiatric history, genetics, personality style such as neuroticism, introversion, personality disorder, history of trauma, low socioeconomic status, low intelligence, and even a family history of trauma.

PTSD, the prototype of traumatic disorders, is accompanied by biological markers such as an increase in blood pressure, pulse, glucocorticoid receptors, T3 and analgesia and reflect a marked sympathetic automatic overdrive, and a decrease in cortisol, alpha 2 adrenergic receptor activity, and stage three and four of sleep. In addition, acute stress is characterized by significant elevation of cortisol. Individuals suffering from chronic PSTD, on the other hand, have blunted plasma cortisol.

Recent and preliminary studies show that PTSD patients in veterans' hospitals have an average of 15 severe traumatic events in their lifetimes. Thus, in comparison to controls, individuals who develop PTSD are more likely to have had previous trauma. Finally, variants of PTSD occur. "Compassion fatigue," a form of traumatic disorder, may develop in health and mental health professionals who care for